PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 02 November 2000 (02.11.00)	
International application No. PCT/GB00/00845	**Applicant's or agent's file reference** P021043WO
International filing date (day/month/year) 08 March 2000 (08.03.00)	**Priority date** (day/month/year) 09 March 1999 (09.03.99)
Applicant GLEN, Alastair, Campbell, Agnew et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

06 October 2000 (06.10.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Juan Cruz
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
P021043WO		
Int rnational application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 00845	08/03/2000	09/03/1999
Applicant		
LAXDALE LIMITED et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search r port, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [ ] as suggested by the applicant.

   [X] because the applicant failed to suggest a figure.

   [ ] because this figure better characteriz s the invention.

   [ ] None of the figures.

CLAIMS

1. An assay for detecting type IV cytosolic phospholipase A_2 ($cPLA_2$) or a protein immunologically homologous to type IV $cPLA_2$, the assay comprising use of red blood cells.

2. An assay according to claim 1 for use in the diagnosis of a disease in which dysfunction of cell signalling systems involving highly unsaturated fatty acids is implicated.

3. An assay according to claim 1 for use in monitoring the effectiveness of medication administered to a patient suffering from a disease in which dysfunction of cell signalling systems involving highly unsaturated fatty acids is implicated

4. An assay according to claim 1 for use in drug development for a disease in which dysfunction of cell signalling systems involving highly unsaturated fatty acids is implicated

5. A method of diagnosis of a disease in which dysfunction of cell signalling systems involving highly unsaturated fatty acids is implicated, said method comprising the detection of type IV cytosolic phospholipase A_2 ($cPLA_2$) protein or a protein immunologically homologous to type IV $cPLA_2$ in or on red blood cells.

6. A method of monitoring the effectiveness of medication administered to a patient suffering from a disease in which dysfunction of cell signalling systems involving highly unsaturated fatty acids is implicated, said method comprising the detection of type IV cytosolic phospholipase A_2 ($cPLA_2$) protein or a protein immunologically homologous to type IV $cPLA_2$ in or on red blood cells.

7. A method of drug development for a disease in which dysfunction of cell signalling systems involving highly unsaturated fatty acids is implicated, said method comprising the detection of type IV cytosolic phospholipase A_2 ($cPLA_2$) protein or a protein immunologically homologous to type IV $cPLA_2$ in or on red blood cells.

8. An assay or method according to any one of claims 1 to 7 wherein the red blood cells are isolated from the human body.

9. An assay or method according to any one of claims 1 to 7 wherein said assay or method comprises use of a whole blood sample without prior isolation of said red blood cells.

10. An assay or method according to any one of claims 2 to 9 wherein said disease is a disease or disease process in which type IV $cPLA_2$ activity or concentration is altered from normal levels.

11. An assay or method according to anyone of claims 2 to 9 wherein said disease is a disease or disease process in which type IV $cPLA_2$ activity or concentration is increased.

12. An assay or method according to any one of claims 2 to 11 wherein the disease is schizophrenia, dyslexia, bipolar or manic depressive illness, cachexia or brain injury.

13. An assay or method according to claim 12 wherein the brain injury is stroke or mechanical brain injury.

14. An assay or method according to any one of claims 1 to 13 wherein the type IV $cPLA_2$ protein or the protein immunologically homologous to type IV $cPLA_2$ has a molecular weight in the range 80 to 110 kDa or in the range 70 to 80 kDa or in the range 50 to 60 kDa.

15. An assay or method according to any one of claims 1 to 13 wherein the type IV $cPLA_2$ protein or the protein immunologically homologous to type IV $cPLA_2$ has a molecular weight in the range 90 to 105 kDa or in the range 70 to 80 kDa or in the range 50 to 60 kDa.

16. An assay or method according to any preceding claim comprising the steps of collecting a sample of blood from a subject and detecting the proteins *ex vivo*.

17. An assay or method according to claim 16 further comprising one or more of the steps of separating the red cells from the other blood components, disrupting the red cells, detecting the proteins either directly or following a protein separation technique.

18. An assay or method according to claim 17 wherein the red cells are disrupted by sonication, freezing, nitrogen cavitation or lysis.

19. An assay or method according to any preceding claim wherein said proteins are detected by immunoassay.

20. An assay or method according to any preceding claim wherein said proteins are detected using an antibody or antibodies that recognise an epitope or epitopes from amino acids 82 to 749 of type IV $cPLA_2$ protein from human monocyte (U937) cells.

21. An assay or method according to any preceding claim wherein said proteins are detected using an antibody or antibodies raised against an epitope or epitopes from amino acids 82 to 749 of type IV $cPLA_2$ protein from human monocyte (U937 cells) or raised against an epitope or epitopes of a synthetic peptide matching amino acids 82 to 749 of type IV $cPLA_2$ protein from human monocyte (U937) cells.

22. An assay or method according to claim 20 or 21 wherein said epitope or epitopes are from a peptide sequence or sequences which comprise the catalytic centre of type IV $cPLA_2$ protein from human monocyte (U937) cells.

23. An assay or method according to claim 20 or 21 wherein said epitope or epitopes are from the peptide sequence of amino acids 241 to 260 of type IV $cPLA_2$ protein from human monocyte (U937) cells.

24. An assay or method according to claim 19 wherein said proteins are detected using an antibody or antibodies raised against an epitope or epitopes from amino acids 1 to 216 of type IV $cPLA_2$ protein from human monocyte (U937) cells.

25. An assay or method according to claims 20, 21, 22, 23 or 24 wherein two or more of the antibodies are used in combination or in sequence to detect the said proteins with the required specificity.

26. An assay or method according to any of claims 1 to 18 for detecting type IV $cPLA_2$ wherein said proteins are detected by substrate assay.

27. A protein obtainable by isolation from red blood cells, said protein being immunologically homologous to type IV $cPLA_2$ and having a molecular weight in the range 80 to 110 kDa or a molecular weight in the range 70 to 80 kDa or a molecular weight in the range 50 to 60 kDa.

28. A protein according to claim 27, said protein being immunologically homologous to type IV $cPLA_2$ and having a molecular weight in the range 90 to 105 kDa or a molecular weight in the range 70 to 80 kDa or a molecular weight in the range 50 to 60 kDa.

29. A diagnostic kit comprising means for disrupting red blood cells and further comprising an antibody or antibodies to a protein obtainable by isolation from red blood cells, said protein being type IV $cPLA_2$ protein or a protein immunologically homologous to type IV $cPLA_2$.

30. A diagnostic kit according to claim 28 wherein said antibody or antibodies is/are raised against an epitope or epitopes from amino acids 82 to 749 of type IV $cPLA_2$ protein from human monocyte (U937) cells.

31. A diagnostic kit according to claim 28 wherein said antibody or antibodies is/are raised against an epitope or epitopes from a peptide sequence or sequences which

comprise the catalytic active centre of type IV $cPLA_2$ protein from human monocyte (U937) cells.

32. A diagnostic kit according to claim 28, 29 or 30 wherein said means for disrupting red blood cells is a means for lysing red blood cells.

33. A diagnostic kit according to claim 28, 29 or 30 which is suitable for near-patient testing.

TENT COOPERATION TRE

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
P021043WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/00845	08/03/2000	09/03/1999
International Patent Classification (IPC) or national classification and IPC G01N33/53		
Applicant LAXDALE LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
06/10/2000	23.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Hinchliffe, P Telephone No. +49 89 2399 8431

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/00845

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-19	as originally filed				
Claims, No.:					
1-33	as received on	04/04/2001	with letter of	04/04/2001	
Drawings, sheets:					
1/4-4/4	as originally filed				

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5,6,8-26 with repect to I.A..

because:

☒ the said international application, or the said claims Nos. 5,6,8-26 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-26,29-33

	No:	Claims	27,28
Inventive step (IS)	Yes:	Claims	1-26,29-33
	No:	Claims	27,28
Industrial applicability (IA)	Yes:	Claims	1-4,7,27-33
	No:	Claims	

2. Citations and explanations
see separate sheet

ITEM III & V

1. The subject matter of claims 1-26 involve using red blood cells (RBCs) in an assay to detect levels of $cPLA_2$. Although the enzyme is known (see D2 as cited in the ISR) this is the first time it has been shown to be associated with RBCs. Consequently the subject matter of these claims fulfills the requirement of Article 33(2) PCT. The closest prior art document is regarded as D1 (as cited in the ISR). This document refers to the detection of a different phospholipase on RBCs and it is alleged that the assay of D1 would inactivate the $cPLA_2$ of the current application. Consequently it would appear to be inventive to look for the $cPLA_2$ on RBCs and consequently the requirement of Article 33(3) PCT is fulfilled for these claims.

2. Claims 27 and 28 are not novel contrary to the requirement of Article 33(2) PCT. Documents D1-D8 (as cited in the ISR) all disclose proteins which fall in to the broad definition found in the said claims:
   D1- protein derived from red blood cells (RBC) stated to be a cPLA (see abstract),
   D2- proteins of 85.2 and 110 kD with $cPLA_2$ activity (see abstract and col.2, line 36),
   D3-purified $cPLA_2$ of 110 kD (see figure 4, table B),
   D4-purified PLA_2 proteins of 60 and 110 kD (see p.4, l.34-42),
   D5-purified PLA_2 proteins of 60 and 110 kD (see p.4, l.26-33),
   D6-purified PLA_2 proteins of 60 and 110 kD (see p.4, l.26-33),
   D7-two cPLAs disclosed, one of 85 kD and the other of 30 kD (see col.2, l.26-27 and l. 48),
   D8-paralogs of $cPLA_2$, however this document is not comprised within the state of the art as the priority document of the present application has been checked and found to be valid.

Information concerning sufficiency of disclosure (Art. 5 PCT): A newly discovered member of a particular protein family should be identified by its amino acid sequence. Immunological identity appears not to be specific enough when a number of proteins share the same function as evidenced by the large number of documents concerning PLAs cited in the search report. Specific antibodies should also be identified by deposit receipts in certain contracting states (EPO).

3. Claims 29-33 refer to kits comprising means for disrupting RBCs and antibodies directed against $cPLA_2$ or immunologically homologous proteins. D4 and D5 both refer to immunoassay of the $cPLA_2$ (see D3 discussion and D4, col.22, l. 47). It is however considered that the skilled person would not take the components used in the immunoassays of these two documents and formulate them into kits involving a RBC disruption reagent as without the inventive knowledge there would be no need to make such a kit. These claims therefore involve an inventive step thus fulfilling the requirements of Article 33(3) PCT.

4. Claims 5,6,8-26, relate, either directly or by implication, to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

CARPMAELS & RANSFORD

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European Patent Office
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D-80298 Munich
GERMANY

YOUR REF

OUR REF P021043WO: PNH/BRC/mmc

4th April 2001

Dear Sirs,

Re: International Patent Application No. PCT/GB00/00845
LAXDALE LIMITED

I refer to your Communication dated 4th December 2000 on this International Application In which a period of three months, kindly extended to four months, was awarded for reply.

In consideration of the Examiner's objections the Applicant proposes to amend claim 1 to recite:

> *Use of red blood cells in an assay for the purpose of detecting type IV cytosolic phospholipase A_2 ($cPLA_2$) or a protein immunologically homologous to type IV $cPLA_2$.*

Dependent claims 2 to 4 and 8 to 26 have been amended accordingly to reflect the new "use" format of claim 1.

Document D1 is concerned with the activity of an unspecified phospholipase A_2 (PLA_2) enzyme and its detection in erythrocytes and blood plasma to predict the course of psoriasis. The Applicant has obtained a full copy of D1 and an English language translation thereof. I enclose copies thereof for the Examiner's perusal.

Inspection of D1 reveals that the assay disclosed therein is concerned only with PLA_2 activity generally. There is no reference to cytosolic PLA_2 enzymes ($cPLA_2$) and

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FACSIMILE MESSAGE

To: **EPO Munich**
Fax No.: **00 49 89 2399 4465**

This fax compris s 7 sheets. If a sheet is missing, or imperfectly received, please contact us immediately (Tel: 020-7242 8692; Fax: 020-7405 4166). If you are not the addressee, pleas contact us immediately and then destroy this fax.

certainly no reference to the specific cytosolic PLA_2 enzyme, namely the type IV cytosolic PLA_2 enzyme, with which the present Application is concerned. There is therefore no disclosure or suggestion in D1 that red blood cells may be used to detect the type IV cytosolic PLA_2 enzyme. It is therefore submitted that the claims of the present Application define subject-matter which is both novel and inventive over D1.

As noted in the preceding paragraph, D1 makes no mention specifically of type IV cytosolic PLA_2 and for this reason alone, the Applicant believes that D1 cannot prejudice the patentability of the present Application. However, the Applicant can provide further evidence that the assay used by the authors of D1 would not even have been "suitable for" detecting type IV cytosolic PLA_2, for the reasons set out below.

D1 detects PLA_2 in erythrocytes and blood plasma using the methodology of Tuzhilin and Saluen'ia which, as noted on page 2 of the translation of D1, involves a preliminary heat treatment of the sample at 60°C for 15 minutes to remove lipase activity. I enclose herewith, for the Examiner's information, a copy of the Russian language original and an English language translation of the methodology of Tuzhilin and Saluen'ia (Laboratornoe Delo, 6, 1795, pp334-5), which shows that the method is stated as being for the determination of PLA_2 activity generally, rather than $cPLA_2$ activity specifically. The Applicant is aware from a further paper (Mayer and Marshall, FASEB Journal, 7, 1993, pp339-348; copy enclosed herewith) that the 85-kDA type IV $cPLA_2$ enzyme denatures when held at 57°C for 5 minutes (see Table 2). It is therefore evident that the methodology used in D1, which involves a heating step at 60°C for 15 minutes, would not detect type IV $cPLA_2$, which denatures when held at 57°C for 5 minutes. The assay of D1 would not therefore even be "suitable for" detecting type IV $cPLA_2$ and is not relevant to the patentability of the subject-matter of the present Application.

With regard to the other cited prior art, particularly D9 and D10, it is submitted that none of this prior art discloses or suggests that red blood cells may be used to detect type IV cytosolic PLA_2. Claims 1 to 26 as amended of the present Application also therefore define patentable subject-matter over this prior art.

With regard to the objections against claims 27 and 28, the Applicant has disclaimed the type IV $cPLA_2$ enzyme disclosed in the prior art (see D2 for example). It is submitted that claims 27 and 28 are therefore novel over the prior art.

Reconsideration of this Application is respectfully requested. A replacement set of claims (replacement pages 20 to 24) are enclosed herewith in triplicate. A copy of the translations and articles referred to above are enclosed with the confirmation copy of this letter.

Yours truly,

P. N. Howard

HOWARD, PAUL NICHOLAS

Enc.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organizati n
International Bureau

(43) International Publication Date
14 September 2000 (14.09.2000)

PCT

(10) International Publication Number
WO 00/54052 A3

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(26) Publication Language: English

(30) Priority Data:
9905417.3 9 March 1999 (09.03.1999) GB
9919952.3 23 August 1999 (23.08.1999) GB

(71) Applicant *(for all designated States except US)*: **LAXDALE LIMITED** [GB/GB]; Kings Park House, Laurelhill Business Park, Stirling FK7 9JQ (GB).

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(74) Agents: **HOWARD, Paul, Nicholas** et al.; Carpmaels & Ransford, 43 Bloomsbury Square, London WC1A 2RA (GB).

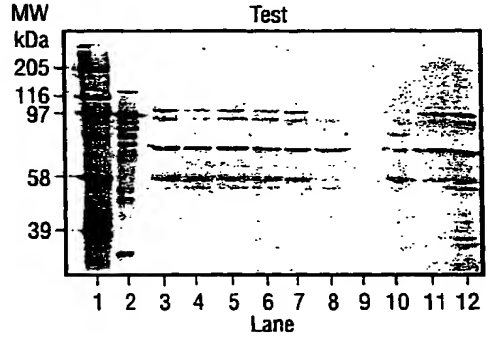
(81) Designated States *(national)*: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

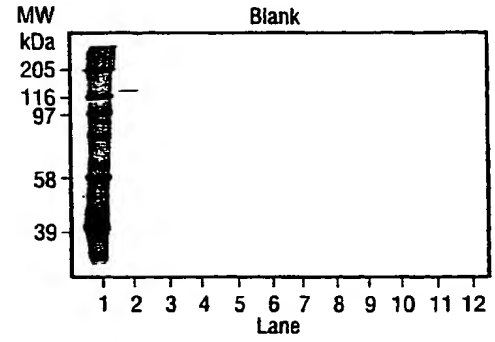
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent

[Continued on next page]

(54) Title: DIAGNOSTIC TEST

(57) Abstract: An assay for detecting type IV cytosolic phospholipase A_2($cPLA_2$) or a protein immunologically homologous to type IV $cPLA_2$, the assay comprising use of red blood cells, particularly for use in the diagnosis of a disease in which dysfunction of cell signalling systems involving highly unsaturated fatty acids is implicated.





WO 00/54052 A3

(AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *With international search report.*

(88) Date of publicati n f the international search rep rt:
21 December 2000

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/GB 00/00845

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/573 G01N33/80 C12N9/20

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N C12Q C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Derwent Publications Ltd., London, GB; AN 1994-284640 XP002143989 FILIMONKOVA N.N.: "Predicting the course of psoriasis by determining the phospholipase A2 activity in the erythrocytes and blood plasma" & RU 2 009 509 C (SVERD SKIN VENERAL DISEASES RES INST), 15 March 1994 (1994-03-15) the whole document --- -/--	1-33

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 September 2000	20/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Pellegrini, P

3

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CLARK J.D. ET AL.: "A novel arachidonic acid-selective cytosolic PLA2 contains a Ca2+ -dependent translocation domain with homology to PKC and GAP" CELL, vol. 65, 1991, pages 1043-1051, XP002143986 cited in the application	27,28
A	abstract	1-26, 29-33
X	ZHU X. ET AL.: "Quantitation of the cytosolic phospholipase A2 (type iv) in isolated human peripheral blood eosinophils by sandwich-ELISA" J. IMMUNOLOG. METH., vol. 199, 1996, pages 119-126, XP002143987	27,28
A	the whole document	1-26, 29-33
X	US 5 354 677 A (KNOPF JOHN L ET AL) 11 October 1994 (1994-10-11) claims	27,28
X	US 5 527 698 A (KNOPF JOHN L ET AL) 18 June 1996 (1996-06-18) claims	27,28
X	US 5 593 878 A (KNOPF JOHN L ET AL) 14 January 1997 (1997-01-14) claims	27,28
X	US 5 279 957 A (GROSS RICHARD) 18 January 1994 (1994-01-18) abstract claim 1	27,28
P,X	R. TODD PICKARD ET AL.: "Molecular cloning of two new human paralogs of 85-KDa cytosolic phospholipase A2" J. BIOL. CHEM., vol. 274, no. 13, 26 March 1999 (1999-03-26), pages 8823-8831, XP002143988 cited in the application	27,28
A	the whole document	1-26, 29-33
A	GATTAZ W.F. ET AL.: "Increased plasma phospholipase A2 activity in schizofrenic patients: reduction after neuroleptic therapy" BIOLOGICAL PSYCHIATRY, vol. 22, 1987, pages 421-426, XP000933408 the whole document	1-33

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/G[redacted]0/00845

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HUDSON C.J. ET AL.: "Phospholipases: in search of a genetic base of schizophrenia" PROSTAGLANDINS, LEUKOTRIENES AND ESSENTIAL FATTY ACIDS, vol. 55, 1996, pages 119-122, XP000925733 the whole document	1-33

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information [redacted] tent family members

Internat[redacted] pplication No
PCT/G[redacted] 00/00845

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
RU 2009509 C	15-03-1994	NONE	
US 5354677 A	11-10-1994	US 5622832 A	22-04-1997
		US 5593878 A	14-01-1997
		US 5527698 A	18-06-1996
		US 5322776 A	21-06-1994
US 5527698 A	18-06-1996	US 5354677 A	11-10-1994
		US 5622832 A	22-04-1997
		US 5593878 A	14-01-1997
		US 5322776 A	21-06-1994
US 5593878 A	14-01-1997	US 5354677 A	11-10-1994
		US 5622832 A	22-04-1997
		US 5527698 A	18-06-1996
		US 5322776 A	21-06-1994
US 5279957 A	18-01-1994	NONE	

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

HOWARD,PAUL N.
CARPMAELS & RANSFORD
43 Bloomsbury Square
London WC1A 2RA
GRANDE BRETAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	23.04.2001
Applicant's or agent's file reference P021043WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/00845	08/03/2000	09/03/1999

Applicant
LAXDALE LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Neumann, M Tel.+49 89 2399-7351

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

DUE: 4-3-01

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
HOWARD,PAUL N.
CARPMAELS & RANSFORD
43 Bloomsbury Square
London WC1A 2RA
GRANDE BRETAGNE

RECEIVED
- 6 DEC 2000
CARPMAELS & RANSFORD
ACTIONED ...

PCT

WRITTEN OPINION

(PCT Rule 66)

Date of mailing *(day/month/year)*	04.12.2000
Applicant's or agent's file reference: P021043WO	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/00845	08/03/2000	09/03/1999

International Patent Classification (IPC) or both national classification and IPC
G01N33/53

Applicant
LAXDALE LIMITED et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain document cited
VII	☒	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 09/07/2001.

Name and mailing address of the international preliminary examining authority:
European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized officer / Examiner
Hinchliffe, P

Formalities officer (incl. extension of time limits)
Saavedra Martinez, V
Telephone No. +49 89 2399 8621

I. Basis of th opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".)*:

Description, pages:

1-19 as originally filed

Claims, No.:

1-33 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-3,5,6,8-15,26 (with repect to I.A.),

because:

☒ the said international application, or the said claims Nos. 1-3,5,6,8-14,26 relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrialapplicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-11,12,14-18,26,27,28 (NO)
Inventive step (IS)	Claims	19-25,29-33 (NO)

Industrial applicability (IA) Claims 1-3,5,6,8-15,26 (NO OPINION)

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
s e separate sheet

ITEM V and VII

1. Claims 1-11,14-18,26 are not novel contrary to the requirement of Article 33(2) PCT.
D1 discloses an assay for predicting the course of psoriasis which involves assaying PLA_2 in a sample of human blood after haemolysis of RBC. Consequently this document teaches a method that involves RBC (as claimed) and furthermore relates to a disease that has a cell signalling system involving highly unsaturated fatty acids is implicated (psoriasis).

2. Claim 12 appears not to be novel contrary to Article 33(2) PCT. D9 and D10 both suggest that the detection of PLA_2 in serum samples of people may be diagnostic of mental illness, in particular Schizophrenia (see D9, introduction). Consequently the assay shown in D9 is novelty destroying for the subject matter of claim 12.

2.2 Claim 13 appears to be novel in the light of the documents cited in the ISR (Article 33(2) PCT), however there is no data to support the allegation that the levels of $cPLA_2$ may be altered by brain injury. Consequently this claim is contrary to the requirements of Article 5 PCT.

3. Claims 27 and 28 are not novel contrary to the requirement of Article 33(2) PCT. Documents D1-D8 (as cited in the ISR) all disclose proteins which fall in to the broad definition found in the said claims:
D1- protein derived from red blood cells (RBC) stated to be a cPLA (see abstract),
D2- proteins of 85.2 and 110 kD with $cPLA_2$ activity (see abstract and col.2, line 36),
D3-purified $cPLA_2$ of 110 kD (see figure 4, table B),
D4-purified PLA_2 proteins of 60 and 110 kD (see p.4, l.34-42),
D5-purified PLA_2 proteins of 60 and 110 kD (see p.4, l.26-33),
D6-purified PLA_2 proteins of 60 and 110 kD (see p.4, l.26-33),
D7-two cPLAs disclosed, one of 85 kD and the other of 30 kD (see col.2, l.26-27 and l. 48),
D8-paralogs of $cPLA_2$, however this document is not comprised within the state of the art as the priority document of the present application has been checked and found to be valid.

4. Claims 19-25 refer to methods of assaying $cPLA_2$ whereby an immunoassay is performed. Both D3 and D4 relate to immunoassays used in the detection of $cPLA_2$ (see D3 discussion and D4, col.22, l. 47). However replacement of a substrate assay, as used in D1, by an immunoassay is obvious and does not involve an inventive step contrary to Article 33(3) PCT.

5. Claims 29-33 refer to kits comprising antibodies directed against $cPLA_2$. D4 and D5 both refer to immunoassay of the $cPLA_2$ (see D3 discussion and D4, col.22, l. 47). It is considered that the skilled person could without inventive activity take the components used in the immunoassays of these two documents and formulate them into kits as claimed. These claims do not therefore involve an inventive step contrary to Article 33(3) PCT.

6. Claims 1-3,5,6,8-15,26, either directly or by implication from claim 16, relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Information concerning sufficiency of disclosure (Art. 5 PCT): A newly discovered member of a particular protein family should be identified by its amino acid sequence. Immunological identity appears not to be specific enough when a number of proteins share the same function as evidenced by the large number of documents concerning PLAs cited in the search report. Specific antibodies should also be identified by deposit receipts in certain contracting states (EPO).